

# Abstract

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## Inhibition of proliferation by omega-3 fatty acids in chemoresistant pancreatic cancer cells.

Hering J, Garrean S, Dekoj TR, Razzak A, Saied A, Trevino J, Babcock TA, Espat NJ.

Department of Surgery, University of Illinois at Chicago, Chicago, Illinois, USA.

**BACKGROUND:** Pancreatic cancer-gemcitabine (GEM) chemoresistance has been demonstrated to be associated with enhanced NF-kB activation and antiapoptotic protein synthesis. The well-known capacity of omega-3 fatty acids (n-3 FAs) to inhibit NF-kB activation and promote cellular apoptosis has the potential to restore or facilitate gemcitabine chemosensitivity.

**METHODS:** Four pancreatic cancer cell lines (MIA PaCa-2, BxPC-3, PANC-1, and L3.6), each with distinct basal NF-kB and differing GEM sensitivity profiles, were administered: 100 uM of (1) n-3FA, (2) n-6FA, (3) GEM, (4) n-3FA + GEM, or (5) n-6FA + GEM for 24 and 48 hours. Proliferation was assessed using the WST-1 assay. To define the mechanism(s) of altered proliferation, electron mobility shift assay for NF-kB activity, western blots of phosphoStat3, phosphoI-kappaB, and poly(ADP-ribose) polymerase (PARP) cleavage were performed in the MIA PaCa-2 cell line.

**RESULTS:** All cell lines demonstrated a time/dose-dependent inhibition of proliferation in response to n-3FA. For MIA PaCa-2 cells, n-3FA and n-3FA + GEM treatment resulted in reduction of I-kB phosphorylation and NF-kB activation when compared with n-6FA control. n-3FA and combination treatment also significantly decreased Stat3 phosphorylation, whereas GEM alone had no effect. n-3FAs and n-3FA + GEM groups demonstrated increased PARP cleavage, mirroring NF-kB activity and Stat3 phosphorylation.

**CONCLUSIONS:** n-3 FA treatment is specifically associated with inhibition of proliferation in these four pancreatic cell lines irrespective of varied gemcitabine resistance. An experimental paradigm to screen for potential contributory mechanism(s) in altered pancreatic cancer cellular proliferation was defined, and using this approach the co-administration of n-3 FA with GEM inhibited GEM-induced NF-kB activation and restored apoptosis in the MIA PaCa-2 cell-line.

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